Papers and Originals

Pathogenesis of the Hyperthyroidism of Graves's Disease*

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Hyperthyroidism occurs in two human disorders. One, which is rare, is the occurrence of a thyroid adenoma which secretes harmfully large amounts of thyroid hormone in the absence of thyroid-stimulating hormone (T.S.H.) (Cope, Rawson, and McArthur, 1947 ; Dobyns and Lennon, 1948). The other, which is common, is the condition known as Graves's disease. The thyroid gland is more uniformly active and there is a tendency for exophthalmos to occur. The discovery that the pituitary gland secretes a T.S.H. (Smith and Smith, 1922) provided a possible explanation for this thyroid overactivity, which enabled the basic cause of the disorder to be placed in the nervous system. It is now apparent, however, that excessive secretion of T.S.H. is not the cause of the hyperthyroidism of Graves's disease, and it seems that the basic defect may lie in the lymphoid system.

Discovery of Long-acting Thyroid Stimulator

The advent of radioactive iodine led to improved methods of assaying T.S.H. One method was based on measurements of blood ^{131}I levels in thyroxine-treated guinea-pigs (Adams and Purves, 1953, 1955, 1957). Intravenous injection of T.S.H. into such animals caused secretion of ^{131}I-labelled thyroid hormone into the blood and the increase in blood radioactivity was related to the amount of T.S.H. injected. When the method was applied to the study of human blood it was found that serum samples from some thyrotoxic patients elicited responses which differed in time course from those elicited by the T.S.H. present in pituitary glands and in sera from hypothyroid people and animals (Adams and Purves, 1956 ; Adams, 1956, 1958). The response elicited by the thyrotoxic serum was prolonged, reaching a maximum value 16 to 24 hours after injection, compared with one and a half to three hours for T.S.H. This observation was soon confirmed by McKenzie (1958a) and Munro (1959), using McKenzie's modification of the assay method, which entails the use of mice instead of guinea-pigs (McKenzie, 1957, 1958b).

Experiments showed that the thyrotoxic sera contained no substance which prolonged the thyroid-stimulating activity of added T.S.H. (Adams, 1958 ; Munro, 1959). The active agent in the thyrotoxic sera was called "long-acting thyroid stimulator" (L.A.T.S.) (Adams, 1961), following the demonstration that it was active in hypophysectomized mice (and therefore did not act by stimulating T.S.H. secretion from the assay animal's pituitary) (Munro, 1959 ; Adams, Purves, and Sirett, 1961) and that it had a half-life of about seven and a half hours after injection into the circulating blood of the rat, compared with 10 to 20 minutes for T.S.H. (McKenzie, 1959 ; Adams, 1960).

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Similarities and Differences Between L.A.T.S. and T.S.H.

Action on the Thyroid.—In addition to its action in increasing thyroid secretion in the assay animal, L.A.T.S. increases thyroid ^{131}I uptake and alters thyroid histology similarly to T.S.H. (McKenzie, 1959, 1960 ; Major and Munro, 1960). L.A.T.S. is a more effective thyroid stimulator in the Adams and Purves and McKenzie assays than is T.S.H. The maximum responses to L.A.T.S. are much larger than the maximum responses to T.S.H., and the dose-response curve for L.A.T.S. is steeper than that for T.S.H., resembling an extension of the initial portion of the T.S.H. curve (Major and Munro, 1960 ; Adams, 1961). The action of L.A.T.S. on the thyroid, therefore, appears to be identical with that which T.S.H. would exert had it the same length of stay in the circulation. This suggests that L.A.T.S. and T.S.H. stimulate the same thyroid mechanism. It has also encouraged the view that L.A.T.S. consists of pituitary T.S.H. abnormally bound to a serum component (Major and Munro, 1962), but other evidence makes this view improbable (see below).

Suppressibility by Administration of Thyroid Hormone.—When T.S.H. can be demonstrated in a patient's blood its level can be shown to decrease after administration of thyroxine to the patient (Adams, 1958, 1965), but this is not the case with L.A.T.S. (Adams, 1958).

Separation of T.S.H. from L.A.T.S.—T.S.H. can be readily separated from L.A.T.S. (Purves and Adams, 1961, 1963) by procedures such as the ethanol-salt percolation of Bates, Garrison, and Howard (1959) or Kennedy's fractional precipitation with acetone (Adams and Kennedy, 1965). These methods free T.S.H. from the serum gamma-globulins. No activity is recoverable by these procedures from sera containing only L.A.T.S.

Failure of T.S.H. Antisera to Neutralize L.A.T.S.—By immunizing animals with T.S.H. preparations made from bovine (Werner, Otero-Ruiz, Seegal, and Bates, 1960 ; Cline, Selenkow, and Brooke, 1960 ; McKenzie and Fishman, 1960) or human (Adams, Kennedy, Purves, and Sirett, 1962) pituitary glands, it is possible to make antisera which can neutralize the hormonal activity of T.S.H. Such antisera are not effective against L.A.T.S., a point of great technological usefulness (Adams, 1965).

Occurrence of Non-specific Responses in the Mouse Assay for T.S.H. and L.A.T.S.

McKenzie's mouse assay method for T.S.H. and L.A.T.S. is not specific for small responses. Thus the activity of serum from euthyroid people (Yamazaki, Noguchi, Sato, and Slingerland, 1961 ; Major and Munro, 1962) and its albumin and globulin fractions (Adams, Kennedy, and Purves, 1965) can be shown to be not attributable to either T.S.H. or L.A.T.S. (Adams *et al.*, 1965 ; Adams, 1965). It is also known that

dextran solutions may show activity in this assay (Munro, 1964).

These non-specific responses are usually small—for example, a 25% increase in the mouse blood ^{131}I content at 10 hours—but are sometimes much larger. The highest 10-hour response observed by me was an increase of 160% (260% response in McKenzie's notation). The mechanism of the non-specific responses is not yet known. There may be more than one.

The specificity of responses to T.S.H. can be readily established by neutralization tests with T.S.H. antisera or by demonstrating suppression by thyroid hormone administration (Adams, 1965). The problem of demonstrating the specificity of small responses to L.A.T.S. is not yet solved, but, in assays of sera, demonstration of increased activity in gamma-globulin concentrates may be helpful.

Mistaken Conclusions Attributable to the Occurrence of Non-specific Responses.—Apart from the notion that T.S.H. and L.A.T.S. were detectable on assay of unfractionated serum from euthyroid people, the early finding by McKenzie and Munro, now retracted, that L.A.T.S. was associated with all the serum-protein fractions, may have been caused by the occurrence of non-specific responses. The mistaken finding that L.A.T.S. was more stable to heating than was T.S.H. (Munro, 1959) is probably another instance. The so-called "short-acting abnormal thyroid-stimulator" (S.A.T.S.) (Adams, Purves, Sirett, and Beaven, 1962) is probably yet another example of some form of non-specific response, possibly of a thyroid-damaging type.

T.S.H. Level in Serum from Euthyroid People

A knowledge of the serum-T.S.H. levels occurring in euthyroidism is necessary for the understanding of the pathogenesis of Graves's disease, especially as in some cases of this disorder the degree of thyroid overactivity is only slight.

Recent work involving the assay of T.S.H. concentrates, using a human T.S.H. standard and devices for checking specificity (Adams and Kennedy, 1965 ; Adams, 1965), supports earlier findings which suggested that the level is several hundred times lower than the highest levels occurring in hypothyroidism (Purves and Adams, 1960). This means that the Adams and Purves and McKenzie assay methods are about 100 times too insensitive to measure the level of T.S.H. occurring in euthyroidism by assay of unfractionated serum.

Evidence Indicating that L.A.T.S. is the Direct Cause of the Hyperthyroidism of Graves's Disease

Incidence.—When allowance is made for non-specific responses it appears that L.A.T.S. is detectable in about 30% of hyperthyroid patients on assay of unfractionated serum (Major and Munro, 1962) and in about 65% of cases on assay of gamma-globulin concentrates (Purves and Adams, 1961). The failure to find L.A.T.S. in all cases of hyperthyroidism is of little significance in view of the insensitivity of the assay method relative to the serum-T.S.H. level occurring in euthyroidism.

There is no convincing evidence of the occurrence of L.A.T.S. in euthyroidism. I have found L.A.T.S. in one case of early myxoedema with no history of hyperthyroidism ; otherwise L.A.T.S. has been found only in Graves's disease.

Range of Activity.—L.A.T.S. has been shown to stimulate the thyroid of the guinea-pig, mouse, rabbit (El Kabir, 1964), and rat (Purves and Adams, 1960). It has also been shown that blood transfused from patients with severe exophthalmos can stimulate the thyroid of a normal person and that the effect is more prolonged than that of injected T.S.H. (Björkman, Denneberg, and Hedenskog, 1961). This indicates that L.A.T.S. stimulates the human thyroid.

Correlation with Thyroid Activity.—In looking for a correlation between clinical thyroid status and serum-L.A.T.S. levels one must consider thyroid efficiency. Thyroid efficiency is impaired by therapeutic measures and it may also be impaired by autoimmune thyroiditis, which occurs frequently in Graves's disease (Buchanan, Alexander, Crooks, Koutras, Wayne, Anderson and Goudie, 1961). However, Major and Munro (1962), studying 71 patients with active hyperthyroidism, found a significant correlation between serum-L.A.T.S. levels, determined by assay, and thyroid activity, measured by ^{131}I tracer tests. This constitutes strong evidence that L.A.T.S. is the direct cause of the hyperthyroidism of Graves's disease.

Evidence that L.A.T.S. does not Originate in the Pituitary Gland

Direct Evidence

Absence of L.A.T.S. from the Pituitary in Graves's Disease.—Pituitary glands taken at necropsy from patients suffering from Graves's disease do not contain detectable L.A.T.S. (Munro, Kilpatrick, Major, and Wilson, 1960 ; Major and Munro, 1962 ; McKenzie, 1962a). Moreover, in two of the four cases studied by Major and Munro and in the one case studied by me no T.S.H. was detectable, a finding which suggests that T.S.H. production had been inhibited, in normal fashion, by the raised blood thyroxine level.

Presence of L.A.T.S. in Blood of People with Hypopituitarism.—L.A.T.S. has been found in the blood of hyperthyroid and euthyroid people suffering from hypopituitarism following hypophysectomy and pituitary-stalk section (McCullagh, Reynolds, and McKenzie, 1960 ; McKenzie, 1962a ; Furth, Becker, Ray, and Kane, 1962). The L.A.T.S. assays were performed without awareness of the existence of non-specific responses (see above), but in at least four of the cases the values for the nine-hour response were high enough to make it probable that L.A.T.S. was present.

Indirect Evidence

This is the evidence that hyperthyroidism and lesser degrees of thyroid activity can occur in the absence of either a functioning pituitary or an autonomous thyroid nodule.

Hyperthyroidism has been observed to occur in patients with clinical hypopituitarism (1) after hypophysectomy (Christensen and Binder, 1962 ; Becker, Furth, Nunez, Horwith, Stokes, Berman, and Ray, 1961) ; (2) after pituitary-stalk section (McCullagh *et al.*, 1960) ; (3) after post-partum pituitary necrosis (Fajans, 1958) ; and (4) after ^{90}Y implantation of the pituitary for acromegaly (Wayne, Koutras, and Alexander, 1964).

In two hyperthyroid patients who were hypophysectomized for mammary carcinoma, Becker (1959) observed thyroid activity to continue at a high level.

In a series of over 350 women who were hypophysectomized for mammary carcinoma, 10 remained euthyroid and had thyroid ^{131}I uptakes in the normal range, not suppressible with triiodothyronine (Pazianos, Benua, Ray, and Pearson, 1960). In two of these patients there was necropsy evidence that the hypophysectomy had been complete and that thyroid nodules were absent.

Evidence that there is no Abnormality of the Pituitary T.S.H. Secretion Mechanism in Graves's Disease

Assay Studies.—Using a T.S.H. concentration method and proving identity of T.S.H. by neutralization tests with antiserum, Adams and Kennedy (1965) were able to demonstrate normal functioning of the T.S.H. secretion mechanism in a woman suffering from Graves's disease and having a high blood-

L.A.T.S. level. In the untreated hyperthyroid state this woman had no demonstrable T.S.H. in her blood. After she had been accidentally rendered myxoedematous by ^{131}I therapy her blood contained T.S.H., which disappeared when she was given thyroxine in suppressive dosage.

Pituitary Cytology Studies.—The work of Ezrin and Murray (1963) is in complete accord with the assay studies, indicating that pituitary T.S.H. secretion is suppressed in the untreated thyrotoxic state, but is increased when a patient with Graves's disease becomes hypothyroid (Ezrin, 1965).

Some Implications of the Theory that L.A.T.S. Causes the Hyperthyroidism of Graves's Disease and that there is no Defect in the Control of T.S.H. Secretion

This theory must be considered to be highly probable in view of the evidence presented above.

Figs. 1 and 2 show the effect of L.A.T.S. on the thyroid-pituitary "negative feed-back" system. The postulated reduction in blood-T.S.H. level in untreated hyperthyroidism has not yet been demonstrated.

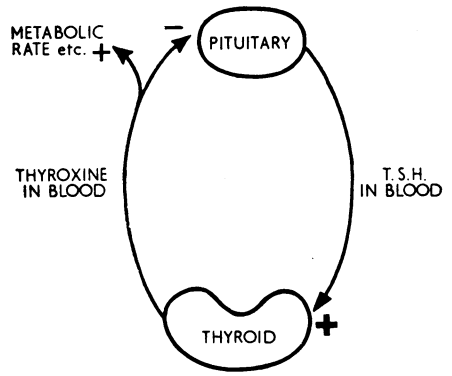

FIG. 1.—Thyroid-pituitary "negative feed-back" system, controlling the blood-thyroxine level in a normal, euthyroid person.

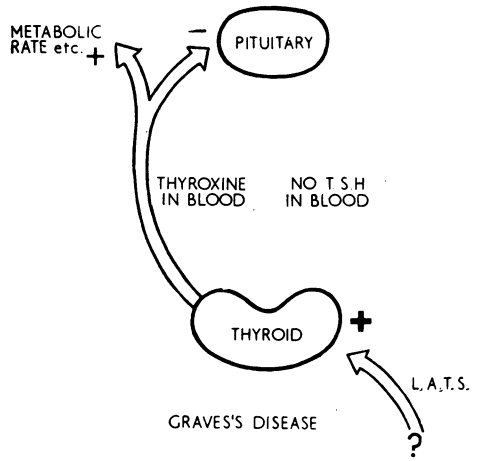

FIG. 2.—Postulated effect of L.A.T.S. in causing a raised blood-thyroxine level in the hyperthyroidism of Graves's disease.

T.S.H. Suppression Test

Failure of thyroid ^{131}I uptake (Greer and Smith, 1954; Werner and Spooner, 1955) or release (Eklund and Ryan, 1962) to be suppressed by the administration of thyroid hormone can be interpreted as indicating the presence of L.A.T.S.

There is no reason to suppose that L.A.T.S. always occurs at levels sufficiently high to cause hyperthyroidism. Evidence suggesting the occurrence of lower levels has been obtained by Werner (1955), who found that triiodothyronine failed to suppress the thyroid activity of some clinically euthyroid patients who had the eye signs of Graves's disease. In these patients the L.A.T.S. levels may not have been high enough to do more than replace the normal action of T.S.H. However, it is also possible that some of these patients were resistant to thyroid hormone (see below).

Restoration of Euthyroidism and Thyroid Suppressibility by Therapy

In view of the narrow range of blood-thyroxine level compatible with euthyroidism and the inevitably wide variation in the amount of thyroid tissue left behind by surgeons performing subtotal thyroidectomy for hyperthyroidism, it is remarkable that in most instances the delicate balance of euthyroidism is restored. The current theory, however, offers an explanation. It is postulated that successful therapy, whether subtotal thyroidectomy, irradiation with ^{131}I, or metabolic impairment with an antithyroid drug, must reduce thyroid efficiency until the L.A.T.S. stimulus is insufficient to produce enough thyroid hormone to maintain suppression of T.S.H. secretion. It is known that T.S.H. can increase the activity of thyrotoxic thyroids (Greer and De Groot, 1956). Once thyroid hormone output is partly dependent on the action of T.S.H., then the blood thyroid hormone level can be adjusted to the euthyroid value.

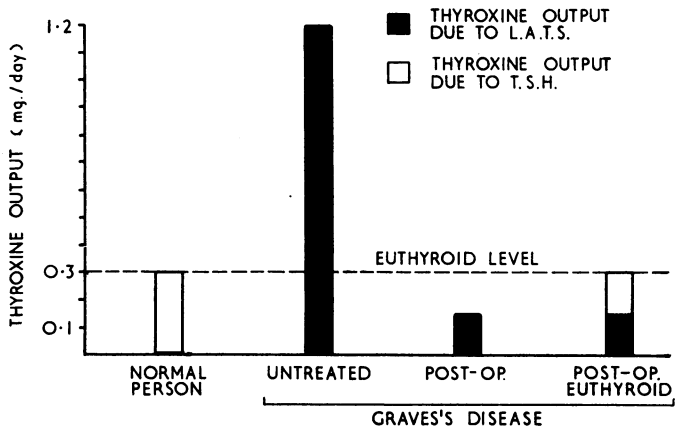

FIG. 3.—Postulated mechanism by which subtotal thyroidectomy restores euthyroidism in hyperthyroid patients, the L.A.T.S. level remaining unchanged.

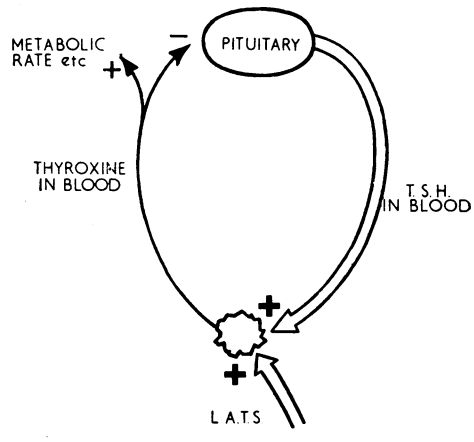

FIG. 4.—Postulated alteration in the thyroid-pituitary "negative feed-back" system after successful treatment of hyperthyroidism.

The hypothesis is illustrated in Figs. 3 and 4. It is supported by the finding that thyroid suppressibility with triiodothyronine returns soon after successful treatment of hyperthyroidism by surgery or ^{131}I administration (Werner, 1956 ; Eckert, Green, Kilpatrick, and Wilson, 1961 ; Hales, Myhill, Oddie, and Rundle, 1961). In the one case tested so far I found T.S.H. to be present in the blood of a Graves's disease patient following successful subtotal thyroidectomy, the T.S.H. disappearing on administration of triiodothyronine. Reduction in thyroid efficiency after treatment of hyperthyroidism has been demonstrated by Eckert *et al.* (1961), who showed that responsiveness to exogenous T.S.H. is reduced.

In addition to the mechanism outlined above, alterations in L.A.T.S. blood level will also have an influence and are probably mainly responsible for the phenomenon of remission and relapse. It seems that there may be a tendency for L.A.T.S. levels to be reduced by surgery and to be transiently increased by ^{131}I therapy, but this is not yet established.

Evidence Suggesting that L.A.T.S. is a Gamma-globulin

There is now general agreement that L.A.T.S. is present in only the gamma-globulin fraction of the serum proteins (Purves and Adams, 1961 ; Adams and Kennedy, 1962 ; McKenzie, 1962b ; Noguchi, Sato, Kurihara, and Ozeki, 1963 ; Kriss, Pleshakov, and Chien, 1964 ; Meek, Jones, Lewis, and Vanderlaan, 1964). Attempts to separate L.A.T.S. from the gamma-globulins have been unsuccessful, and while it remains impossible to prove that L.A.T.S. is not composed of something firmly attached to a gamma-globulin, there is strong evidence that it does not contain pituitary T.S.H. (see above). The following evidence suggests that L.A.T.S. is itself a gamma-globulin.

(*a*) The hormonal activity of L.A.T.S. can be neutralized by incubation with antibodies to euthyroid human gamma-globulin (Kriss *et al.*, 1964 ; Adams and Sharard, 1965 ; Dorrington and Munro, 1965).

(*b*) Preliminary studies indicate that the heat-stability of L.A.T.S. is similar to that of a human antibody to thyroglobulin in that both withstand heating at 56° C. and are inactivated by heating at 70° C., whereas human T.S.H. is only partially inactivated at 70° C. (McGiven, Adams, and Purves, 1965).

(*c*) A transient form of hyperthyroidism may occur in the babies of women with Graves's disease (Sclare, 1960). McKenzie (1964) has found L.A.T.S. in the serum of affected babies. The most likely explanation of the phenomenon is that it is caused by placental transfer of L.A.T.S. from the maternal to the foetal circulation. The duration of the disorder fits well with the known half-life of maternal gamma-globulins in the baby (Adams, Lord, and Stevely, 1964).

(*d*) Serum-L.A.T.S. levels tend to be reduced by prolonged administration of corticosteroids in high dosage (Kriss *et al.*, 1964 ; Green, Snyder, and Solomon, 1963). The tendency for hyperthyroidism to remit during pregnancy (Munro, 1964) may be another illustration of the same effect.

(*e*) Tests of the effect on L.A.T.S. of procedures known to fragment gamma-globulins (Porter, 1963) are under way in several laboratories and at the time of writing have failed to indicate that L.A.T.S. is not a gamma-globulin. Comparison of the situation of antibody activity in gamma-globulin molecules with the situation of thyroid-stimulating activity in L.A.T.S. will be of great interest.

Should future work continue to indicate that L.A.T.S. is a gamma-globulin it would be better renamed "thyroid-stimulating globulin" (T.S.G.).

Speculation on Nature of Fundamental Defect Causing Hyperthyroidism of Graves's Disease

The following speculation is not based on sufficient evidence to constitute a hypothesis, but I hope that it may stimulate research.

If L.A.T.S. is a thyroid-stimulating gamma-globulin it may be produced in response to an antigenic stimulus. The pioneering work of Doniach and Roitt (1957) and Witebsky, Rose, Terplan, Paine, and Egan (1957) revolutionized medical thinking by establishing that antibodies to thyroid-gland components occur in man. It is now known that thyroid antibodies are common in Graves's disease, as well as in autoimmune thyroiditis and myxoedema (Roitt and Doniach, 1960). The titre of thyroid antibodies rises transiently after ^{131}I therapy, which apparently intensifies the antigenic stimulus (Irvine, 1964). I and others have observed L.A.T.S. levels to respond to ^{131}I therapy in the same way, suggesting that production of L.A.T.S. is dependent on an antigenic stimulus from the thyroid. However, this conclusion is tenuous, as the response of L.A.T.S. levels to ^{131}I therapy has not yet been studied formally.

If L.A.T.S. is an antibody against a thyroid-gland component, then its antigen may be the site with which T.S.H. interacts. There is no evidence for this, but it would explain the possession by L.A.T.S. of its thyroid-stimulating property.

Irvine (1964) has observed that while irradiation with ^{131}I consistently increases the titre of detectable thyroid antibodies, it has little tendency to provoke the appearance of thyroid antibodies not already detectable. This suggests that the ability to form the various thyroid antibodies in response to the appropriate antigenic stimulus is not universal, but is confined to certain individuals. Irvine concludes that thyroid autoimmunity may be a "disorder of immunological tolerance." This important observation suggests, by analogy, that the fundamental defect in the hyperthyroidism of Graves's disease may be the ability of the lymphoid system to produce L.A.T.S. in response to an antigenic stimulus from the thyroid.

It is obviously most important that the effect of ^{131}I therapy on L.A.T.S. levels be studied further.

Resistance to Thyroid Hormone.—Occasional patients with Graves's disease appear to be resistant to their own, or administered, thyroid hormone—for example, cases described by Falconer and Alexander (1951), Adams, Purves, Sirett, and Beaven (1962), and Becker (1959). The reason for this is quite unknown. The finding of Premachandra, Ray, Hirata, and Blumenthal (1963) that circulating thyroid hormone may interact with circulating antibodies to thyroglobulin may be relevant to the problem.

Possible Relevance to Other Disorders.—If L.A.T.S. proves to be a gamma-globulin, then it will be likely that other metabolically active gamma-globulins occur. This would allow the occurrence of much more subtle metabolic disruptions in autoimmunity than could occur were the action of autoantibodies confined to cell destruction and histamine release. The occurrence of a transient neonatal form of myasthenia gravis, analogous to congenital thyrotoxicosis, suggests that a metabolically active gamma-globulin may play a pathogenic part in this disorder, as already postulated by Simpson (1960).

Exophthalmos

The absence of exophthalmos in hyperthyroidism due to toxic adenoma suggests that it is not related to thyroid overactivity but may be related to thyroid autoimmunity. L.A.T.S. levels do not correlate with degree of exophthalmos (Major and Munro, 1962), a finding which is against the possibility that L.A.T.S. is the direct cause of exophthalmos. T.S.H. almost certainly does not play a part in human exophthalmos, as its levels in the plasma are high in untreated myxoedema (where exophthalmos is rare) and are probably very low or absent in the untreated hyperthyroidism of Graves's disease, where exophthalmos is common.

Human exophthalmos does not seem to be caused by a factor from the pituitary, as it has occurred in a hypophysectomized patient (Furth *et al.*, 1962).

There have been reports of striking alleviation of exophthalmos following orbital decompression performed on the opposite side (Falconer and Alexander, 1951) and also after hypophysectomy (Albeaux-Fernet, Guiot, Braun, and Romani, 1955 ; Furth *et al.*, 1962). I have observed a modest but crucially important reduction in proptosis to occur in the two weeks following a subtotal thyroidectomy. The only common factor in these three situations appears to be surgical stress, which apparently has an inconsistent tendency to cause exophthalmos to remit.

Catz (1965) reports good results in the treatment of malignant exophthalmos by thyroid ablation, performed by ^{131}I administration. In my view this is at present the best treatment for desperate cases of this sort. It is possible that Catz's findings indicate that exophthalmos is caused by an autoantibody to a thyroid-gland component.

Summary

A thyroid-stimulating substance, distinct from pituitary thyroid-stimulating hormone (T.S.H.), occurs in the blood of patients suffering from Graves's disease. This substance is at present called " long-acting thyroid stimulator " (L.A.T.S.).

There is evidence that L.A.T.S. is not of pituitary origin and that it is the direct cause of the hyperthyroidism of Graves's disease. There is also evidence, both from bioassays and from studies of pituitary cytology, that there is no defect in the control of T.S.H. secretion in Graves's disease, the secretion being inhibited in the untreated hyperthyroid state. These findings explain how therapeutic measures which reduce thyroid efficiency can restore euthyroidism. The mechanism of the diagnostic T.S.H.-suppression tests also becomes apparent.

At present the evidence suggests that L.A.T.S. is a gamma-globulin which stimulates the thyroid in a manner similar to that of T.S.H. L.A.T.S. may be an autoantibody against a thyroid-gland component.

I have great pleasure in expressing my indebtedness to Professor G. M. Wilson, who, together with Dr. H. D. Purves and Professor E. B. Astwood, is responsible for the pursuit of this line of investigation.

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